

chain bonds :

3-11 11-12 11-13 18-19

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 13-14 13-17 14-15 15-16  
16-17

exact/norm bonds :

1-2 1-6 2-3 3-4 3-11 4-5 11-12 14-15 18-19

exact bonds :

11-13 13-14 13-17 15-16 16-17

normalized bonds :

5-6 5-7 6-10 7-8 8-9 9-10

isolated ring systems :

containing 13 :

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom

11:CLASS 12:CLASS 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom

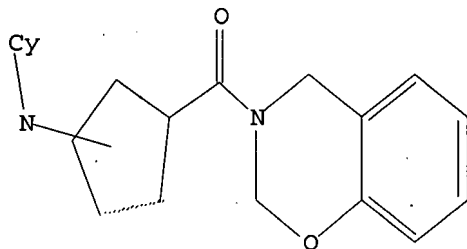
21:Atom

L1 STRUCTURE UPLOADED

=&gt; d l1

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=&gt; s l1

SAMPLE SEARCH INITIATED 14:29:03 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 180 TO ITERATE

100.0% PROCESSED 180 ITERATIONS

0 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 2796 TO 4404

PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=&gt; s l1 sss full

FULL SEARCH INITIATED 14:29:11 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 3740 TO ITERATE

Habte

09/12/2007

100.0% PROCESSED 3740 ITERATIONS  
SEARCH TIME: 00.00.01

17 ANSWERS

L3 17 SEA SSS FUL L1

=&gt; file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

172.10

172.31

FILE 'CAPLUS' ENTERED AT 14:29:15 ON 12 SEP 2007

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FILE COVERS 1907 - 12 Sep 2007 VOL 147 ISS 12

FILE LAST UPDATED: 11 Sep 2007 (20070911/ED)

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<http://www.cas.org/infopolicy.html>

=&gt; s 13

L4 1 L3

=&gt; d ibib abs hitstr

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

ACCESSION NUMBER: 2004:799448 CAPLUS

DOCUMENT NUMBER: 141:314341

TITLE: Preparation of (tetrahydropyran-4-yl)amino)cyclopentanecarbonyl-substituted fused azaheterocycles as modulators of cytokine receptors such as CCR2

INVENTOR(S): Goble, Stephen D.; Pasternak, Alexander; Mills, Sander

PATENT ASSIGNEE(S): G.; Zhou, Changyou; Yang, Lihu

SOURCE: Merck & Co. Inc., USA

LANGUAGE: PCT Int. Appl., 142 pp.

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION: CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004/082616	A2	2004/0930	WO 2004-US7831	2004/0312
WO 2004/082616	A3	2005/0421		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004/222341	A1	2004/0930	AU 2004-222341	2004/0312
CA 2519297	A1	2004/0930	CA 2004-2519297	2004/0312
EP 1606280	A2	2005/1221	EP 2004-720505	2004/0312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
CN 1826334	A	2006/0830	CN 2004-80013280	2004/0312
JP 2007524590	T	2007/0830	JP 2006-507192	2004/0312
IN 2005DN04099	A	2007/0831	IN 2005-DN4099	2005/0912
US 2006/178363	A1	2006/0810	US 2005-550111	2005/0919
PRIORITY APPL. INFO.			US 2003-456046P	P 2003/0318
			WO 2004-US7831	A 2004/0312

OTHER SOURCE(S): MARPAT 141:314341

G1

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Compds. I [A = R<sup>2</sup>2C, C(=O), NR<sup>2</sup>, O; B = R<sup>2</sup>2C, O, S(=O), SO<sub>2</sub>, NSO<sub>2</sub>R<sup>1</sup>, NC(=O)R<sup>1</sup>, NC(=O)NR<sup>1</sup>, C(=O); D, X = C, N; E = (CH<sub>2</sub>)<sub>n</sub>; G = CH<sub>2</sub>CH, CH<sub>2</sub>CH<sub>2</sub>;

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

Y = O, R<sup>1</sup>2N, S, S(=O), SO<sub>2</sub>, R<sup>1</sup>12C, etc.; n = 0-2; R<sup>1</sup> = H, NC, (un)substituted alkyl, heterocyclyl, Ph, R<sup>1</sup>22N, R<sup>1</sup>3C(=O)N(R<sup>1</sup>2), R<sup>1</sup>4SO<sub>2</sub>N(R<sup>1</sup>2), R<sup>1</sup>1C(=O), R<sup>1</sup>22NC(=O); R<sup>2</sup> = H, alkyl, P, HO, heterocyclyl, R<sup>1</sup>3C(=O)NH, etc.; R<sup>3</sup>, R<sup>4</sup> = absent, H, (un)substituted alkyl, HO, Cl, O, etc.; R<sup>5</sup> = (un)substituted alkyl, alkoxy, alkylcarbonyl, alkylthio, pyridyl, etc.; R<sup>6</sup> = H, alkyl, (un)substituted alkylcarbonylalkyl; R<sup>1</sup>1 = HO, H, (un)substituted alkyl, alkoxy, cycloalkyl, benzyl, phenyl; R<sup>1</sup>2 = alkyl, (un)substituted alkyl, benzyl, Ph, cycloalkyl; R<sup>1</sup>3 = H, (un)substituted alkyl, alkoxy, benzyl, Ph, cycloalkyl; R<sup>1</sup>4 = H, HO, (un)substituted alkyl, benzyl, Ph, cycloalkyl; R<sup>1</sup>5 = H, (un)substituted alkyl; R<sup>1</sup>6 = H, (un)substituted alkyl, alkoxy, cycloalkyl, P, HO, etc.; R<sup>1</sup>7 = H, HO, (un)substituted alkyl, alkoxy, R<sup>1</sup>1C(=O); R<sup>1</sup>8 = H, F, (un)substituted alkyl, cycloalkoxy, alkoxy; R<sup>1</sup>6 and either R<sup>1</sup>7 or R<sup>1</sup>8 may be joined in a ring such as II are prepd. as modulators of cytokine receptors such as CCR2 for the treatment of inflammatory and immune system disorders such as rheumatoid arthritis. Coupling of (tert-butoxy)(trifluoromethyl)benzylamine III and nonracemic (tetrahydropyran-4-yl)amino)cyclopentanecarboxylic acid IV followed by cleavage of the tert-Bu group, cyclocondensation with paraformaldehyde, and cleavage of the trifluoroacetamide yields II as its hydrochloride salt. III is prepd. by nucleophilic substitution of 2-fluoro-5-(trifluoromethyl)benzonitrile with potassium tert-butoxide followed by hydrogenation of the nitrile moiety. IV is prepd. by Boc protection of the amine moiety of V, benzylation of the carboxylic acid group, cleavage of the Boc group, reductive amination of the amine with tetrahydropyran-4-one, trifluoroacetylation of the secondary amine, stereoselective alkylation of the ester with potassium bis(trimethylsilyl)amide and iso-Pr iodide, and hydrogenolysis of the benzyl ester; a second route to IV is also described. Comps. of the invention inhibit CCR2 with IC<sub>50</sub> values of < 1 μM (no data).

IT 765296-96-6P 765296-97-7P 765296-98-8P 765296-99-9P 765297-00-5P 765297-01-6P 765297-21-0P 765297-32-3P 765297-33-4P 765297-34-5P 765297-35-6P 765297-36-7P 765297-37-8P 765297-52-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

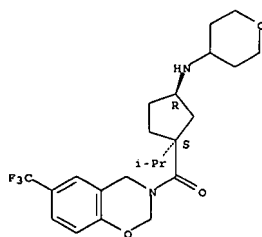
(preparation of (tetrahydropyran-4-yl)amino)cyclopentanecarbonyl-substituted fused azaheterocycles as modulators of cytokine receptors such as CCR2 for the treatment of inflammatory and immune system diseases such as rheumatoid arthritis)

RN 765296-96-6 CAPLUS

CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-(1-methylethyl)-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)-9C1] (CA INDEX NAME)

Absolute stereochemistry.

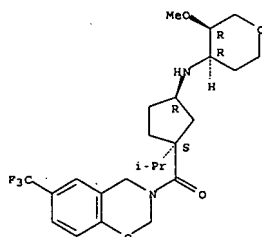
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 765296-97-7 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-2-O-methyl-3-[[[(1R,3S)-3-(1-methylethyl)-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]amino]-9C1] (CA INDEX NAME)

Absolute stereochemistry.

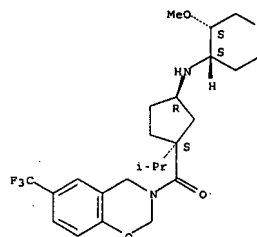


RN 765296-98-8 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-4-O-methyl-3-[[[(1R,3S)-3-(1-methylethyl)-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]amino]-9C1] (CA INDEX NAME)

Absolute stereochemistry.

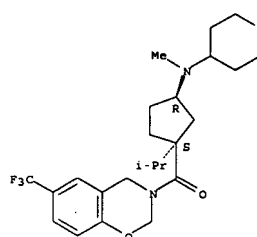
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 765296-99-9 CAPLUS

CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-(1-methylethyl)-3-(methyl(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)-9C1] (CA INDEX NAME)

Absolute stereochemistry.

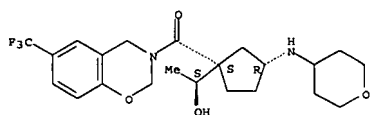


RN 765297-00-5 CAPLUS

CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-(1-methylethyl)-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)-9C1] (CA INDEX NAME)

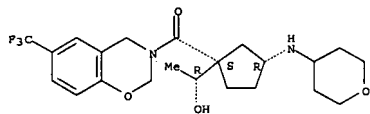
Absolute stereochemistry.

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



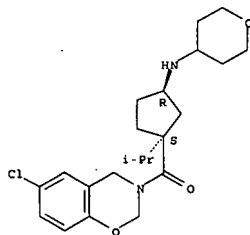
RN 765297-01-6 CAPLUS  
 CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-[(1R)-1-hydroxyethyl]-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

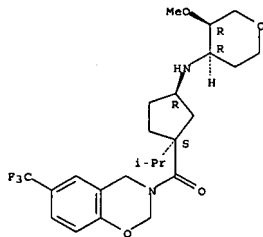


RN 765297-21-0 CAPLUS  
 CN 2H-1,3-Benzoxazine, 6-chloro-3,4-dihydro-3-[[[(1S,3R)-1-[(1-methylethyl)-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



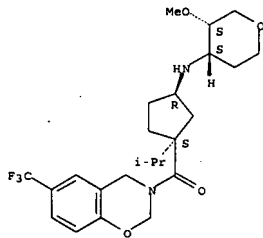
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



● HCl

RN 765297-34-5 CAPLUS  
 CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-2-O-methyl-3-[[[(1R,3S)-3-[(1-methylethyl)-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]amino]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



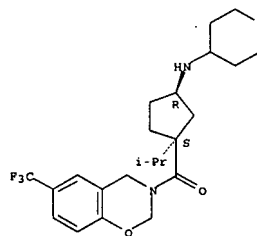
● HCl

RN 765297-35-6 CAPLUS  
 CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-[(1-methylethyl)-3-[(methyl(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 765297-32-3 CAPLUS  
 CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-[(1-methylethyl)-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



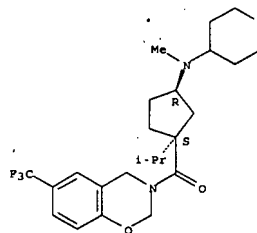
● HCl

RN 765297-33-4 CAPLUS  
 CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-2-O-methyl-3-[[[(1R,3S)-3-[(1-methylethyl)-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]amino]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

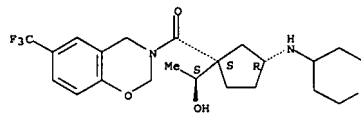
Absolute stereochemistry.



● HCl

RN 765297-36-7 CAPLUS  
 CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-[(1S)-1-hydroxyethyl]-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

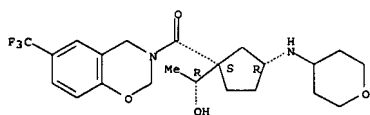


● HCl

RN 765297-37-8 CAPLUS  
 CN 2H-1,3-Benzoxazine, 3,4-dihydro-3-[[[(1S,3R)-1-[(1R)-1-hydroxyethyl]-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]-6-(trifluoromethyl)]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

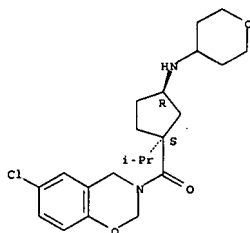
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



● HCl

RN 765297-52-7 CAPLUS  
 CN 2H-1,3-Benzoxazine, 6-chloro-3,4-dihydro-3-[[[(1S,3R)-1-(1-methylethyl)-3-[(tetrahydro-2H-pyran-4-yl)amino]cyclopentyl]carbonyl]]-, monohydrochloride (9CI) (CA INDEX NAME)

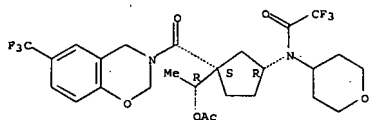
Absolute stereochemistry.



● HCl

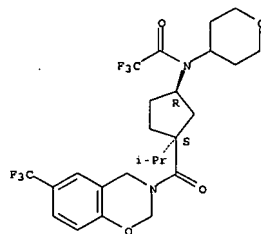
IT 765297-60-7P 765297-65-2P 765297-67-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of  
 (tetrahydropyran-4-ylamino)cyclopentanecarbonyl-substituted fused azaheterocycles as modulators of cytokine receptors such as CCR2 for the treatment of inflammatory and immune system diseases such as rheumatoid arthritis)  
 RN 765297-60-7 CAPLUS

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



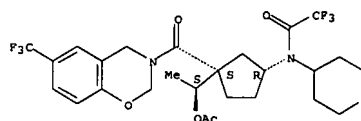
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)  
 CN Acetamide, 2,2,2-trifluoro-N-[(1R,3S)-3-(1-methylethyl)-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]-N-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 765297-65-2 CAPLUS  
 CN Acetamide,  
 N-[(1R,3S)-3-[(1S)-1-(acetyloxy)ethyl]-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]-2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 765297-67-4 CAPLUS  
 CN Acetamide,  
 N-[(1R,3S)-3-[(1R)-1-(acetyloxy)ethyl]-3-[[6-(trifluoromethyl)-2H-1,3-benzoxazin-3(4H)-yl]carbonyl]cyclopentyl]-2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.